Published Ahead of Print on October 4, 2004 as 10.1200/JCO.2004.08.080

VOLUME 22 · NUMBER 22 · NOVEMBER 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Quality of Life in Ovarian Cancer Patients: Comparison of Paclitaxel Plus Cisplatin, With Cyclophosphamide Plus Cisplatin in a Randomized Study

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Submitted August 12, 2003; accepted September 1, 2004.

Supported by a core grant from the National Cancer Institute of Canada, and in part by funding from Bristol Myers-Squibb and the EORTC Data Centre.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2222-1/$20.00

DOI: 10.1200/JCO.2004.08.080

ABSTRACT

Purpose
Formal quality-of-life (QOL) assessments may contribute important information on patient symptoms. Despite many trials of systemic chemotherapy in ovarian cancer, reports of its effect on QOL are few.

Patients and Methods
QOL was assessed in an Intergroup randomized trial comparing paclitaxel plus cisplatin to cyclophosphamide plus cisplatin in women with advanced ovarian cancer. One hundred fifty-two eligible patients accrued in Canada completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and a trial-specific checklist at baseline (after surgical debulking) and at regular intervals during and after chemotherapy. Mean change scores over time in the two arms were calculated.

Results
Compliance with QOL questionnaire completion was excellent (81% to 93%). In general, deterioration was seen in the QOL domains immediately after chemotherapy (day 8 of cycle 1), followed by clinically meaningful improvements compared with baseline (change scores ≥ 10) in both arms during the treatment period in a number of domains and items, including global QOL, emotional function, social function, fatigue, pain, sleep, constipation, appetite, abdominal swelling, and abdominal cramps. Improvements in global QOL persisted for the duration of follow-up. More neurosensory effects and myalgia were documented in the paclitaxel arm; however, this did not adversely affect global or other domains of QOL and improved once chemotherapy was completed.

Conclusion
Improvement from baseline in QOL measures was seen in both treatment arms. The greater neurologic and muscle toxicity of paclitaxel did not adversely influence QOL. QOL data can contribute useful information on the experience of symptoms and their time course, which may assist patients and physicians in their discussion about the anticipated effects of therapy.

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INTRODUCTION

Quality of life is of great importance in assessing the impact of therapy in patients with locally advanced cancers. Women with advanced epithelial ovarian cancer frequently are treated with, and demonstrate a response to chemotherapy, but have only a modest chance of long-term survival; only approximately 10% to 20% of women with advanced disease are progression free 5 years after their diagnosis.[1-3] Numerous randomized studies comparing various chemotherapy regimens have been completed in the last two decades. Results from these trials have been summarized in several recent

meta-analyses or systematic reviews.[1-3] They concluded that platinum-containing combination regimens were superior to the same regimen without platinum, that carboplatin and cisplatin were similarly efficacious, and that there was some evidence that platinum combination treatment was superior to single-agent platinum. As a result, cisplatin plus cyclophosphamide emerged as the standard of care to which new regimens would be compared. Subsequent to these trials, a series of studies have been completed that examined the benefits of adding paclitaxel to first-line therapy. Four trials compared first-line paclitaxel versus nonpaclitaxel therapy and yielded conflicting results.[4-7] In two studies (Gynecologic Oncology Group 111, Intergroup trial[4,5]) the paclitaxel arm was clearly superior in terms of progression-free and overall survival. In the remaining two studies (Gynecologic Oncology Group 132, International Collaborative Ovarian Neoplasm Group 3[6,7]), no such advantage to the experimental arm could be documented. Many have sought to explain these discordant observations without convincing success. Because the positive trials were the first to be done, the majority of the ovarian cancer community has moved to adopt paclitaxel plus a platinum compound as the standard of care, and certainly the standard for the next generation of studies.

Despite the fact that numerous comparative therapeutic studies have been completed, there are relatively few reports of comparisons of the quality-of-life (QOL) effects of these differing therapies. As noted, given that most women with advanced ovarian cancer are not cured and many regimens have similar efficacy, differences in QOL may help determine which regimen is preferred. Furthermore, systematic documentation of the QOL experience of patients enrolled onto clinical trials may assist in providing information to future nontrial patients regarding the expected effects of therapy as they make their treatment choices. The QOL literature is more scant in ovarian cancer than in other common malignancies,[8,9] with relatively few publications detailing QOL effects of chemotherapy,[10,11] and others exploring specific QOL issues, including fatigue[12] and survivorship issues.[13] A recently published randomized trial of cisplatin plus paclitaxel versus carboplatin plus paclitaxel[14] includes QOL results in 679 patients with advanced ovarian cancer, also using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30); tumor efficacy was comparable, but the toxicity profile was better with carboplatin, with small but significant differences in QOL scores in favor of that regimen.

This article reports the results of QOL assessments obtained at baseline and throughout therapy in Canadian women with a diagnosis of advanced epithelial ovarian cancer enrolled onto an Intergroup multicenter trial of paclitaxel plus cisplatin (TP) versus cyclophosphamide plus cisplatin (CP). Specifically, we compared the QOL experience between the two study arms. The results of the study, indicating improved progression-free and overall survival with paclitaxel plus platinum, were reported in May 2000.[5] Since that date, an update of more mature survival information shows a continued significant survival advantage to the paclitaxel arm (relative hazard of death, 0.75; 95% CI, 0.63 to 0.90).[15]

PATIENTS AND METHODS

Randomized Trial

The Intergroup phase III comparison of TP and CP in advanced epithelial ovarian cancer (National Cancer Institute of Canada Clinical Trials Group [NCIC CTG] OV.10/EORTC 55931) was a joint study of the EORTC Gynecological Cancer Cooperative Group, NCIC CTG, Nordic Gynecological Cancer Study Groups, and Scottish Gynecologic Cancer Trials Group. The primary objective of the study was to determine whether the substitution of paclitaxel given during 3 hours for cyclophosphamide in combination with cisplatin would improve the progression-free survival of first-line therapy of advanced ovarian cancer. Secondary end points included response rate, overall survival, toxicity, QOL, and cost effectiveness. Patients with epithelial ovarian carcinoma, International Federation of Gynecology and Obstetrics stages IIb, IIc, III, and IV were randomly assigned to receive six cycles of either TP (paclitaxel 175 mg/m^2 administered during a 3-hour infusion and cisplatin 75 mg/m^2 administered intravenously every 3 weeks) or CP (cyclophosphamide 750 mg/m^2 and cisplatin 75 mg/m^2 administered intravenously every 3 weeks). A total of 680 patients (668 eligible) were accrued in a 16-month period from 1994 to 1995. As noted, the study demonstrated that TP produced significantly superior survival compared with the standard CP arm.

Quality of Life Assessment

QOL was assessed using the EORTC QLQ-C 30(+3) questionnaire and a trial-specific checklist. The QLQ-C30+3 is a core questionnaire consisting of 33 items that assess five functional domains (physical, role, cognitive, emotional, and social), three symptom domains (fatigue, pain, and nausea or vomiting), six single items (dyspnea, sleep, appetite, constipation, diarrhea, and financial), and a global QOL scale. The core questionnaire, known as the QLQ-C30, has been psychometrically validated in numerous cancer patients.[16] The version of the QLQ-C30 questionnaire used in this study included three additional items (questions 31, 32, and 33) of a developmental nature. The trial-specific checklist was specifically designed for this study and consists of a series of 11 questions that provide additional details on ovarian cancer symptom-related distress (see Appendix for a sample of the checklist).

QOL assessments were to be done at baseline and on day 1 (prechemotherapy) of each cycle of chemotherapy, on day 8 of cycle 1, and every 3 months after the completion of treatment until disease progression or for a total of 2 years after the end of chemotherapy, whichever came first. Although the study called for six cycles of chemotherapy, patients with an incomplete response could be offered another one to three cycles at the discretion of their oncologist; QOL information was collected on day 1 of those cycles as well.

Statistical Analyses

The QLQ-C30 responses were scored and analyzed according to algorithms in a scoring manual supplied by the EORTC Study Group on Quality of Life.[17] Each question in the trial-specific

checklist was treated as a single item. All raw scores were transformed first to a 0 to 100 scale. For the functioning domains and global QOL scale, higher scores indicate better functioning, whereas in the symptom domains and single items, higher scores indicate the symptom is more severe.

Questionnaire completion rates at baseline and during the protocol treatment were calculated for all patients enrolled onto the study. Mean baseline scores for each of the domains and items in the core and trial-specific questionnaires for each of the treatment groups were first calculated. At each assessment point postbaseline and for each domain and item, the change score from baseline was then calculated as the difference between the score at this time point and the baseline score for all patients who had scores recorded at both this time and baseline. The mean change score for all patients at a given time was calculated and compared between the two treatment groups using the Wilcoxon rank sum test. A positive change in mean scores for the functional domains (physical, role, cognitive, emotional, and social) as well as the global QOL score indicated improvement, whereas a positive change in mean scores for the symptom domains from the core questionnaire and the symptom items from the trial-specific check list indicated worsening. As a secondary analysis of several domains and issues of interest (global QOL, muscle pain, and sensation in fingers or toes), growth curves[18] were constructed using repeated measures analysis.

Because the patients from the Nordic and Scottish groups did not participate in the QOL study and a large portion of EORTC patients did not complete the baseline questionnaires (40% rate of completion), only the patients enrolled by NCIC CTG were included in the comparative analyses.

RESULTS

Patient Population

Between 1994 and 1995, 680 patients were accrued onto the study; 160 of these (152 eligible) were accrued in Canada by NCIC CTG participating institutions. Table 1

Table 1. Patient Characteristics per Treatment Arm (all patients and NCIC CTG subset)

Characteristic	Cyclophosphamide Plus Cisplatin				Paclitaxel Plus Cisplatin			
	All (n = 338)		Canadian (n = 73)		All (n = 342)		Canadian (n = 79)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	58		60		58		58	
Range	22-85		36-75		23-79		34-79	
Performance status								
0	171	50.5	10	14	159	46.5	11	14
1	125	37	43	59	138	40.5	46	58
2	40	12	19	26	40	11.5	20	25
3	2	0.5	1	1	5	1.5	2	3
FIGO stage								
IIb	8	2.5	1	1	10	3	0	0
IIc	15	4.5	1	1	12	3.5	1	1
III	245	72.5	59	81	256	75	66	84
IV	70	20.5	12	16	64	18.5	12	15
Cell type								
Serous adenocarcinoma	221	62.5	47	64	235	68.5	53	67
Endometrioid adenocarcinoma	46	13.5	11	15	31	9	13	16
Mucinous adenocarcinoma	18	5.5	5	7	12	3.5	3	4
Clear cell adenocarcinoma	18	5.5	4	5	15	4.5	2	3
Anaplastic or undifferentiated	29	8.5	1	1	29	8.5	2	3
Mixed cell type	9	2.5	5	7	16	4.5	4	5
Nonepithelial ovarian cancer	0	0	0	0	2	0.5	0	0
Cytology proven only	2	0.5	0	0	0	0	0	0
Unknown or missing	4	1	0	0	2	0.5	1	1
Tumor grade								
Well differentiated	29	8.5	7	10	28	8	7	9
Moderately differentiated	86	25.5	22	30	92	27	20	25
Poorly differentiated or undifferentiated	192	57	39	53	197	57.5	46	58
Not applicable or unknown	31	9	5	7	25	7.5	6	8
Amount of residual disease								
No macroscopic	53	15.5	8	11	60	17.5	8	12
Macroscopic, optimally debulked	63	18.5	16	22	72	21	18	23
Macroscopic, not optimally debulked	221	65.5	49	67	209	61	53	67
Missing	1	0.5	0	0	1	0.5	0	0

Abbreviations: NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; FIGO, International Federation of Gynecology and Obstetrics.

shows the demographic and clinical characteristics of the overall population, as well as the Canadian subset, by treatment arm. They were comparable with the exception of baseline performance status. Fewer Canadian patients with baseline ECOG performance status of 0 were randomly assigned than in the overall study population. Most patients (93%) had a laparotomy before study entry, and had residual disease more than 1 cm (suboptimally debulked, 67%) before beginning treatment. The most frequent sites of disease at time of random assignment were pelvis (66%), ascites (43%), nodes (24%), pleural effusion (24%), liver (20%), and abdomen (17%).

Compliance With QOL Completion

Tables 2 and 3 show the compliance, by study arm, for completion of QOL questionnaires during therapy at the protocol-prescribed intervals for NCIC CTG patients. Eight of the 160 Canadian patients were ineligible for the study, leaving 152 eligible patients included in the QOL analysis. Compliance for NCIC CTG patients was excellent (81% to 93%) at all time points, aside from day 8 in cycle 1 for which QOL data were logistically more difficult to collect, and was not enforced for the entire duration of the study. Because of a higher proportion of patients completing all cycles of chemotherapy in the TP arm (88% TP patients completed at least six cycles versus 77% of CP patients), there was a somewhat greater number of patients providing on-treatment QOL information in this arm in comparison with the CP arm.

Table 2. Compliance: Cyclophosphamide Plus Cisplatin Arm (NCIC CTG subset)

Cycle	Expected	Received	% of Expected	% of Total No. Entered Onto Trial
Baseline	73	72	98.6	98.6
Day 8 of cycle 1	73	51	69.9	69.9
Day 1 of cycle 2	71	69	97.2	94.5
Day 1 of cycle 3	68	62	91.2	84.9
Day 1 of cycle 4	63	59	93.7	80.8
Day 1 of cycle 5	59	50	84.7	68.5
Day 1 of cycle 6	56	52	92.9	71.2
Day 1 of cycle 7	15	15	100.0	20.5
Day 1 of cycle 8	11	10	90.9	13.7
Day 1 of cycle 9	11	10	90.9	13.7
Month 3	50	40	80.0	54.8
Month 6	36	33	91.7	45.2
Month 9	27	22	81.5	30.1
Month 12	20	19	95.0	26.0
Month 15	13	12	92.3	16.4
Month 18	17	14	82.4	19.2
Month 21	8	7	87.5	9.6
Month 24	8	6	75.0	8.2

Abbreviations: NCIC CTG, National Cancer Institute of Canada Clinical Trials Group.

Table 3. Compliance: Paclitaxel Plus Cisplatin Arm (NCIC CTG subset)

Cycle	Expected	Received	% of Expected	% of Total No. Entered Onto Trial
Baseline	79	79	100.0	100.0
Day 8 of cycle 1	79	57	72.2	72.2
Day 1 of cycle 2	77	72	93.5	91.1
Day 1 of cycle 3	77	70	90.9	88.6
Day 1 of cycle 4	74	70	94.6	88.6
Day 1 of cycle 5	73	68	93.2	86.1
Day 1 of cycle 6	70	61	87.1	77.2
Day 1 of cycle 7	22	21	95.5	26.6
Day 1 of cycle 8	19	18	94.7	22.8
Day 1 of cycle 9	13	10	76.9	12.7
Month 3	64	53	82.8	67.1
Month 6	58	47	81.0	59.5
Month 9	48	36	75.0	45.6
Month 12	39	32	82.1	40.5
Month 15	28	22	78.6	27.8
Month 18	27	19	70.4	24.1
Month 21	19	19	100.0	24.1
Month 24	21	15	71.4	19.0

Abbreviations: NCIC CTG, National Cancer Institute of Canada Clinical Trials Group.

Effect of Treatment on QOL

The mean and standard deviation of the baseline scores for each domain and item are given in Table 4. Patients in both study arms showed impairment at baseline of global QOL, role function, and social function, as well as a significant burden of symptoms, particularly fatigue, loss of appetite, sleep problems, pain, swelling in abdomen, and stomach cramps. The baseline QOL scores were comparable between the two arms, with the exception of more frequent urination in the CP arm (mean, 25.7 versus 13.9; $P = .03$) and marginally better social functioning in the CP arm (mean, 54.9 versus 44.2; $P = .05$).

Tables 5, 6, and 7 list the mean change scores from baseline by treatment arm for each domain and item during therapy and up to 24 months after completion of treatment. For most items, the pattern of change in mean scores is similar over time in both study arms, with few instances of significant differences observed. In general, there was deterioration seen in the QOL domains immediately after chemotherapy (day 8 of cycle 1), followed by clinically meaningful improvements compared with baseline (change scores ≥ 10) in both arms in a number of domains and items. Improvement was observed by cycle 2 of chemotherapy, and included global QOL (Fig 1), emotional function, social function, fatigue, pain, sleep, constipation, appetite, abdominal swelling, and abdominal cramps. Improvements in global QOL (change scores ranging from 10 to 20) persisted for the duration of follow-up; there was a marginal advantage in global QOL in patients in the CP arm during chemotherapy, which was not seen in the postchemotherapy period.

Table 4. Mean Baseline Scores of QOL Domains and Symptoms by Study Arm

QOL Domain or Symptom	Cyclophosphamide Plus Cisplatin			Paclitaxel Plus Cisplatin		
	No.	Mean Baseline Score	SD	No.	Mean Baseline Score	SD
QLQ-C30 Domains						
Physical	72	67.9	28.38	78	71.9	26.14
Role	71	55.6	40.13	77	52.6	41.28
Emotional	71	62.8	27.67	79	65.0	26.63
Cognitive	70	77.9	26.73	79	79.8	24.56
Social	72	44.2	34.39	78	54.9	33.24
Global QOL	71	43.3	27.34	79	50.0	24.89
Fatigue	72	50.2	28.03	79	49.5	24.06
Nausea	72	16.4	23.82	79	13.7	22.76
Pain	72	41.7	28.53	79	38.2	28.01
Dyspnea	72	17.1	23.06	79	17.7	23.17
Sleep	72	40.7	33.20	79	32.9	32.24
Appetite	71	42.7	34.82	79	33.3	34.18
Constipation	70	22.9	32.37	78	31.2	35.37
Diarrhea	70	17.1	30.43	79	14.8	25.46
Financial	71	17.4	29.74	79	23.6	33.82
Trial-specific symptom checklist items						
Soreness in mouth or throat	72	6.94	20.12	79	7.2	19.0
Muscle aches and pains	72	21.3	29.2	79	16.9	26.6
Shortness of breath	70	9.5	19.8	79	11.8	22.7
Swelling in abdomen	72	36.1	35.7	78	28.9	35.5
Frequent urination	72	13.9	24.2	79	25.7	33.3
Loss of bladder control	70	4.3	12.6	78	9.0	22.6
Stomach cramps	72	29.6	32.4	79	27.9	32.2
Sensation in figures or toes	72	6.5	19.1	79	3.0	10.9
Hair loss	69	1.9	12.6	77	2.2	9.9
Medicine for pain	72	35.2	39.5	78	32.5	33.5
Pain after medication	64	15.6	20.6	71	14.6	22.4

Abbreviations: QOL, quality of life; SD, standard deviation; QLQ-C30, Quality of Life Questionnaire C30.

Although both cisplatin and paclitaxel may be associated with neurotoxicity, there were significant differences in the change scores for both muscle pain and neurotoxicity (sensation in fingers or toes), with worse symptoms during chemotherapy in the TP arm. Although muscle pain tended to improve (lower scores) in the CP arm, it worsened (higher scores) over the same time frame in the TP arm. These differences were both clinically and statistically significant. As shown in Fig 2, the differences in muscle pain disappeared toward the end of chemotherapy. Sensory changes followed a similar pattern (Fig 3). Increases in mean change scores reflective of more severe symptoms were seen in the TP arm early during treatment (by cycle 3). Although symptoms also increased in the CP arm, these occurred later (by cycle 8) and were less severe. With follow-up after completion of therapy, the differences between arms seemed to disappear after a year, as shown in Fig 3.

Growth curves of the three domains and issues of specific interest (global QOL, muscle pain, and sensation in fingers or toes) confirmed the above-mentioned conclusions: there were no differences between the two study arms at any of the time points within the first year for global QOL (Fig 1B); worse muscle pain for TP at the 3-month time point only; and worse sensation in fingers or toes at 3, 6, 9, and 12 months (data beyond 12 months were not included).

DISCUSSION

This trial was undertaken primarily to determine if TP offered superior progression-free and overall survival outcomes compared with a standard of CP in women with newly diagnosed advanced epithelial ovarian cancer. The results were convincing in demonstrating highly significant increases in both progression-free and overall survival for the study arm (TP; approximately 4- and 10-month increases of median survivals, respectively).[5] QOL measures were undertaken to provide a longitudinal view of patient-reported symptoms, both disease and treatment related, as well as providing a general assessment of global well-being and functional status of patients treated with both regimens. If this study had demonstrated therapeutic equivalence between the two regimens, the QOL data would have been critical to the decision-making process in

Table 5. Mean Change Scores for Each Domain/Symptom by Study Arm: Part A

	Physical Function		Role Function		Emotional Function		Cognitive Function		Social Function		Global QOL		Fatigue		Nausea	
Cycle	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP
Day 8 cycle 1	−17.5	−20.0	−24.4	−14.7	6.4	1.8	−3.3	−5.1	−6.7	−10.8	−9.3	−9.8	12.1	14.5	24.8	22.4
Day 1 cycle 2	−1.8	3.1	−5.5	−1.5	11.7	12.6	3.2	4.3	15.6	14.0	13.9	9.9	−9.3	−9.3	−8.1*	0.2
Day 1 cycle 3	4.9	2.0	−0.9	10.3	17.0	13.2	7.2	2.4	22.1	9.4	19.6	15.8	−14.1	−11.3	−1.9	−0.2
Day 1 cycle 4	9.7*	0.2	7.1	5.4	14.5	12.2	8.9	3.6	27.7	16.4	17.8	12.1	−15.4	−13.6	−2.0	−4.1
Day 1 cycle 5	11.1*	0.1	6.2	10.3	14.2	11.4	11.8*	0.8	27.1	15.9	18.9	11.2	−14.3	−8.2	0	0.8
Day 1 cycle 6	9.4	2.2	7.3	12.9	14.0	12.6	7.0	2.0	24.3	12.1	17.2	10.2	−9.9	−10.1	3.3	1.6
Day 1 cycle 7	18.6	1.5	7.1	21.0	15.4	15.1	13.1*	−4.2	26.2	17.5	17.9	13.1	−13.5	−12.2	9.5	0.8
Day 1 cycle 8	16.0	−0.3	10.0	26.7	15.8	21.3	8.3	1.8	23.3	17.6	10.2	8.3	−5.6	−14.2	11.7	0
Day 1 cycle 9	12.0	4.0	5.6	33.3	13.3	13.3	8.3	3.3	21.7	35.0	10.2	16.7	−4.4	−10.0	20.0	−5.0
Month 3	10.2	2.0	13.9	15.6	11.0	14.7	3.2	8.0	25.4	25.8	15.8	18.3	−10.8	−20.0	−5.3	−9.3
Month 6	14.5	10.2	17.7	19.3	11.7	15.6	10.8	8.0	26.3	30.3	15.0	18.1	−18.1	−22.0	−4.8	−11.2
Month 9	6.7	11.4	14.3	28.6	8.3*	20.6	7.1	9.7	20.6	25.5	11.5	21.8	−13.2	−25.9	−6.4	−6.0
Month 12	14.2	11.6	16.7	32.3	22.1	21.4	15.7	4.2	22.2	28.6	23.5	15.9	−21.6	−24.7	−7.4	−4.7
Month 15	18.0	17.1	30.0	30.0	14.4	14.4	13.6	0	31.8	28.0	18.9	19.3	−22.2	−22.2	−6.7	−3.8
Month 18	15.7	12.9	38.5	21.9	13.1	16.7	10.7	7.4	35.7	26.8	25.0	12.5	−29.4	−16.7	−8.3	−5.6
Month 21	25.7	16.7	35.7	26.7	21.4	20.6	2.8	3.7	61.9	34.2	30.9	22.8	−27.0	−23.4	−4.8	−6.1
Month 24	20.0	21.3	50.0	30.0	31.9	15.0	3.3	4.4	55.6	34.4	40.3	18.9	−29.6	−14.8	−8.3	−5.6

Abbreviations: QOL, quality of life; CP, cyclophosphamide plus cisplatin; TP, paclitaxel plus cisplatin.
*$P < .05$.

recommending one regimen over another. Even though the difference in efficacy was pronounced, the QOL data can still play a useful role in describing the impact of treatment in terms that might help inform patients about the experience of therapy. Our data show that over the course of treatment, both regimens are associated with a meaningful improvement in most of the domains and symptoms of QOL. The persistence of improvement while enrolled onto the study suggests that this is due to the palliative effect of chemotherapy on the tumor, which one would assume would continue until the time of clinical relapse. Despite the shorter progression-free survival with CP, the global QOL improvements were just as prompt during therapy as those seen with TP.

Table 6. Mean Change Scores for Each Domain/Symptom by Study Arm: Part B

	Pain		Dyspnea		Sleep		Appetite		Constipation		Diarrhea		Financial	
Cycle	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP
Day 8 cycle 1	−12.1	−0.9	−2.9	6.4	7.8	13.5	13.8	18.6	13.3	7.7	−0.8	12.2	3.0	−5.8
Day 1 cycle 2	−22.0	−13.6	−8.1	−3.8	−3.0	−0.9	−22.4	−14.3	−5.6	−6.7	−13.0	−3.8	0.5	−2.8
Day 1 cycle 3	−27.3*	−16.4	−4.4	−4.8	−10.9	−2.9	−25.0	−15.5	−7.5	−6.4	−5.8	−9.7	−2.8	−2.9
Day 1 cycle 4	−29.6*	−17.4	−3.4	−5.8	−14.9	−6.8	−24.6	−16.4	−8.9	−11.9	−10.1	−6.4	1.2	−1.4
Day 1 cycle 5	−29.6	−17.9	4.1	−5.6	−18.4*	−4.6	−25.9	−17.7	−7.1	−10.0	−10.6	−8.0	−2.8	0
Day 1 cycle 6	−33.7*	−16.7	6.5	0	−17.0*	−1.1	−24.2	−13.1	−10.2	−14.8	−8.2	−2.2	1.3	−4.4
Day 1 cycle 7	−32.1	−23.0	10.3	−1.6	−14.3*	11.1	−31.0	−27.0	−16.7	−18.3	−7.1	−3.2	9.5	−6.4
Day 1 cycle 8	−28.3	−22.2	20.0*	1.8	−26.7*	−1.8	−33.3	−33.3	−3.3	−22.2	−3.3	−11.8	3.3	−3.7
Day 1 cycle 9	−28.3	−23.3	26.7*	3.3	−23.3	0	−26.7	−36.7	−3.3	−13.3	3.3	−16.7	16.7	3.3
Month 3	−18.0	−22.1	1.8	−6.5	−8.8	−19.6	−25.4	−22.9	−2.7	−20.9	−5.4	−5.1	−0.9	−4.6
Month 6	−23.1	−17.4	0	−4.5	−17.8	−8.9	−25.8	−22.2	0	−10.9	−6.7	−6.5	1.1	−3.0
Month 9	−14.3	−23.6	3.2	−5.6	−12.7	−9.3	−22.2	−20.4	−11.1	−18.1	3.2*	−14.8	−1.7	−13.0
Month 12	−18.5	−19.3	3.7	−1.0	−11.1	−1.0	−20.4	−13.5	−7.4	−21.9	−7.4	−4.2	−9.3	−13.5
Month 15	−28.8	−21.2	6.7	−1.5	−16.7	−13.6	−23.3	−15.2	−6.1	−20.6	3.0	−9.1	−9.1	−3.0
Month 18	−34.5	−14.8	−2.4	1.8	−23.8	−1.9	−31.0	−16.7	−2.4	−22.2	−4.8	0	−11.9	−9.3
Month 21	−40.5	−16.7	−4.8	−5.3	−23.8	0	−33.3	−19.3	14.3*	−19.3	−4.8	−7.1	−19.0	−12.3
Month 24	−38.9	−23.3	5.6	4.4	−33.3*	2.2	−33.3	−11.1	0	−8.9	5.6	−8.9	−22.2	−15.6

Abbreviations: CP, cyclophosphamide plus cisplatin; TP, paclitaxel plus cisplatin.
*$P < .05$.

Table 7. Mean Change Score for Checklist Items by Arm

Cycle	Sore Mouth		Muscle Pain		Shortness of Breath		Abdominal Swelling		Frequent Urination		Loss of Bladder Control		Stomach Cramps		Sensation Fingers or Toes		Hair Loss		Pain Medicine		Pain After Medication	
	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP	CP	TP
Day 8 cycle 1	2.1	1.3	−1.4*	17.3	0.7	7.1	−14.5	−9.2	4.4	−9.6	2.2	−2.6	−4.3	3.3	2.1	5.8	4.4	10.5	−14.2	−4.6	2.9	−1.6
Day 1 cycle 2	−2.6	0.9	−6.6	4.3	−1.6	−3.3	−23.7	−14	0.5*	−11.1	−0.5	−1.9	−17.7*	−4.4	−5.6*	5.2	41.9*	70.6	−22.6*	−11.8	−4.8	−3.4
Day 1 cycle 3	0.0	0.0	−11.7*	10.8	−1.7	−0.5	−26.0	−20.6	−0.6*	−14.2	−1.8	0.0	−18.1	−18.1	−4.0*	14.5	43.5	43.5	−23.0	−13.5	−5.8	−2.4
Day 1 cycle 4	−0.6	−2.5	−10.7*	13.0	0.6	−2.4	−23.4	−21.1	−1.2*	−14.0	1.8	−1.0	−17.0	−19.6	−2.3*	23.5	37.6	34.9	−26.3	−17.2	−8.1	−1.4
Day 1 cycle 5	2.0	−1.0	−10.2*	9.2	6.8	−0.5	−25.2	−17.4	−6.1	−13.6	−0.7	1.6	−9.5	−16.7	0*	25.8	38.2	37.6	−25.2*	−12	−13.3*	−0.7
Day 1 cycle 6	11.6	1.6	−10.5	11.5	6.7	1.1	−26.8	−19.4	−4.6	−15.8	2.7	1.1	−14.0	−19.7	4.0*	39.9	31.2	32.8	−26.1	−16.1	−10.5	−3.8
Day 1 cycle 7	−2.4	−4.8	−4.8	3.2	5.1	−9.5	−28.6	−25	−7.1	−23.8	7.1	−1.7	−21.4	−25.4	11.9*	44.4	45.2	52.6	−28.6	−25	−16.7	−2.1
Day 1 cycle 8	−3.3	−5.6	10.0	3.7	3.3	−3.7	−23.3	−29.4	−6.7	−24.1	−6.7	−5.9	−23.3	−31.5	26.7	50	33.3	44.4	−33.3	−33.3	−12.5	−7.1
Day 1 cycle 9	−3.7	−3.3	−7.4	3.3	12.5	3.3	−25.9	−30	−11.1	−29.6	−11.1	−3.3	−25.9	−26.7	33.3	46.7	20.8	40	−33.3	−33.3	−16.7	−8.3
Month 3	0.0	−4.5	14.4	11.5	5.3*	−5.8	−18.0	−20.5	−5.3	−17.9	−5.3	−3.2	−9.9	−20.3	46.5	58.3	2.9	10.5	−21.1	−19.6	0	−3.9
Month 6	4.3	−3.6	1.1	11.6	0.0	−0.7	−16.1	−12.9	−2.2*	−18.8	−2.2	0.0	−10.8	−16.3	18.3*	41.1	4.3	3.0	−21.5	−17.4	0	−1.1
Month 9	0.0	−5.6	11.1	2.9	−1.6	−6.5	−11.1	−20	0.0*	−25.9	0.0	−3.8	−3.2*	−27.8	27.0	30.6	0	−2.9	−28.6	−21.9	−8.9	−9.5
Month 12	2.0	−4.3	11.8	10.8	4.2	−3.2	−18.8	−16.1	−3.9	−17.2	−3.9	2.2	−3.9	−21.5	5.9	30	0	3.3	−27.5	−16.1	−10.0	−1.3
Month 15	3.0	−1.5	−12.1	1.5	3.0	−4.6	−30.3	−16.7	3.0*	−24.2	3.0	4.5	−9.1	−19.7	18.2	21.2	3.0	0	−30.3	−15.2	0	−1.8
Month 18	0.0	−5.6	−7.1	5.6	2.4	−3.9	−25.6	−13.7	5.1	−14.8	5.1	1.9	−4.8	−20.4	9.5	20.4	0	0	−33.3*	−14.8	−3.7	0
Month 21	0.0	−5.3	−4.8	5.3	4.8	−9.3	−33.3	−18.5	4.8	−17.5	4.8	5.3	−19.0	−22.8	14.3	15.8	−4.8	0	−16.7	−15.8	−6.7	0
Month 24	0.0	0.0	0.0	2.2	5.6	2.2	−5.6	−6.7	5.6	−11.1	5.6	4.4	−22.2	−13.3	33.3	20	−5.6	2.2	44.4	−15.6	−13.3	5.1

Abbreviations: CP, cyclophosphamide plus cisplatin; TP, paclitaxel plus cisplatin.
*$P < .05$.

With respect to the impact of toxicity, the results of our study suggest that QOL information was consistent with the reported toxicity[19]: more neurosensory effects and myalgia were documented in the TP arm. The completeness of the longitudinal measures of these symptoms up to 24 months after treatment provides some reassurance that, with time, both arms come together in the magnitude of these effects: neurosensory changes were similar (as measured by mean change scores from baseline) by about 12 months after treatment was complete. Differences in myalgia between the arms disappeared by about 3 months after therapy. Furthermore, despite the differences in the individual symptom experience between the arms, there was no apparent adverse impact of these on the main domains of QOL: mean scores for global QOL, and physical, emotional, social, and role functions were similar over time in both arms.

Both of these observations (the recovery from significant treatment-related symptoms and the lack of apparent impact on global functioning) are clinically useful data that were not previously documented, and that may assist both the woman and the physician in the

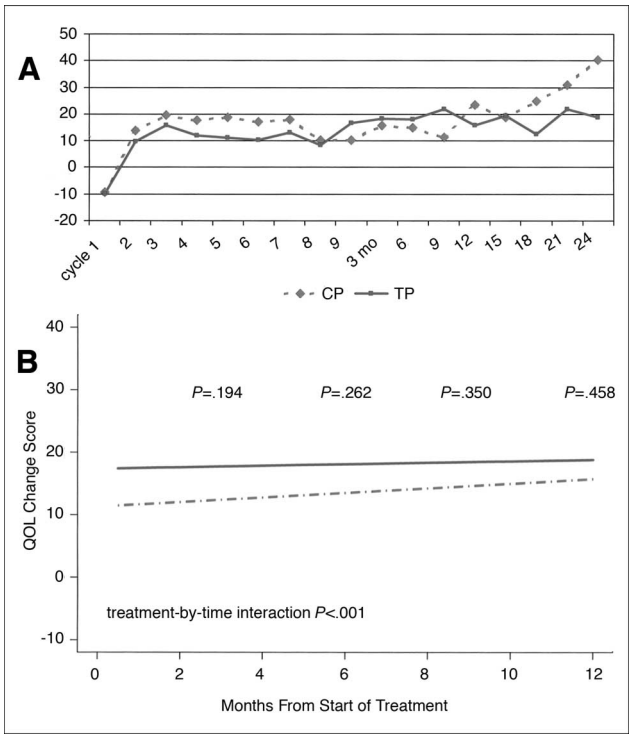

Fig 1. (A) Mean change score by arm: global quality of life (QOL). Positive change indicates improvement. (B) OV.10 NCIC CTG data global QOL fitted growth curve. Solid curve, CP; dashed curve, TP. NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; CP, cisplatin and cyclophosphamide; TP, cisplatin and paclitaxel.

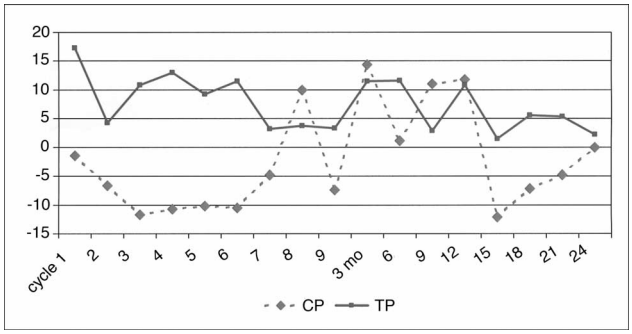

Fig 2. Mean change score by arm: muscle pain. CP, cisplatin and cyclophosphamide; TP, cisplatin and paclitaxel.

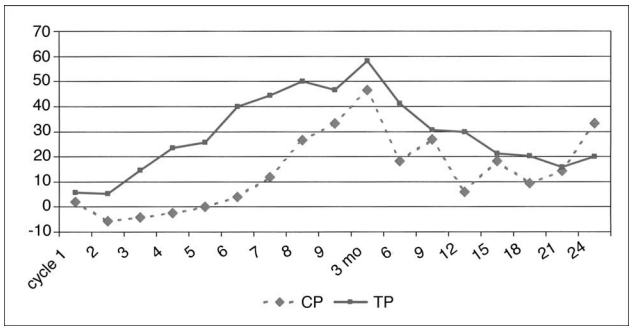

Fig 3. Mean change score by arm: sensation in fingers or toes. CP, cisplatin and cyclophosphamide; TP, cisplatin and paclitaxel.

discussion about the anticipated effects of the proposed chemotherapy treatments.

As in any QOL analysis, the data need to be interpreted bearing in mind potential study limitations. Limitations of this study are that it represents QOL information only from the Canadian subset of patients (ie, 22% of patients accrued in the study). Although these patients were comparable in their baseline characteristics with the patients accrued in other countries, some confounding variables unique to the Canadian centers (eg, supportive care measures employed) may have had an impact on the QOL scores. The baseline QOL scores and symptoms may have been due to the effect of surgery rather than ovarian cancer itself; thus, improvements in QOL and symptoms may have occurred even in the absence of chemotherapy. Only patients still participating in the study (who have not experienced disease progression) are providing QOL data, and as time goes by, this becomes a small proportion of the initial patient cohort. Thus, maintenance of QOL improvement is not seen in all patients entering onto the study. However, one should not assume that the QOL improvements are confined only to responders; in an analysis of QOL data from a breast cancer study, we have demonstrated a gradient effect of QOL response and tumor response, with QOL improvements seen also in patients with stable disease.[20]

Since this study was completed, additional randomized studies have been conducted with the substitution of carboplatin for cisplatin in the paclitaxel regimen.[14,21,22] Those trials have not shown any differences in efficacy between the two platinums, but have consistently demonstrated less neurotoxicity in the carboplatin plus paclitaxel arms as measured by traditional toxicity grading. For these reasons, carboplatin plus paclitaxel is widely regarded as the current standard of care. Nevertheless, our results demonstrate QOL benefits of both chemotherapeutic regimens.

Acknowledgment

We thank Eric Bacon for his excellent statistical assistance, Keith James, MD, for the coordination of the study, and the many patients, clinical research associates, and investigators who contributed to the study.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix: Trial-Specific Check List Used in the National Cancer Institute of Canada Gyncologic Cancer Intergroup OV.10

During the Past Week:	Not at All	A Little	Quite a Bit	Very Much
1. Has soreness in your mouth or throat interfered with eating or drinking?	1	2	3	4
2. Have aches or pains in your muscles been a problem?	1	2	3	4
3. Has shortness of breath interfered with your activities?	1	2	3	4
4. Has swelling in your abdomen bothered you?	1	2	3	4
5. Have you been bothered by frequent urination?	1	2	3	4
6. Have you had loss of bladder control?	1	2	3	4
7. Have you been bothered by stomach cramps?	1	2	3	4
8. Have changes in sensation in your fingers or toes been a problem?	1	2	3	4
9. Have you been bothered by hair loss?	1	2	3	4
10. Did you take medicine for pain?	1	2	3	4
11. If you took medicine for pain did any pain remain?	1	2	3	4

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